Amendments to the Drawings:

The attached sheets of drawings include changes to Figure 2. The attached sheets replace the original sheets of Figure 2. Figure 2 previously omitted sequence identification numbers.

Attachment: Replacement sheets
Annotated Sheets Showing Changes

Amendments to the Sequence Listing:

Please insert the enclosed paper copy of the revised "Sequence Listing" into the application after the section entitled "Abstract of the Disclosure."

REMARKS

In a non-final Office Action dated February 10, 2006 the Examiner in charge of this case rejected the claims of this application. Claims 1-8 are currently pending in the application; Claims 4-8 are withdrawn from consideration as being directed to a non-elected invention; Claims 1-3 are rejected under 35 U.S.C. §112, 1st ¶. Applicants respond by submitting the amendments and comments set forth hereinbelow. Based on this submission, reconsideration of the merits of this patent application is respectfully requested.

Election/Restrictions

Although applicants continue to traverse the Examiner requirement for restriction, the finality of the requirement is acknowledged. Accordingly, applicants reserve the right to file a divisional application drawn to non-elected Claims 4-8.

Information Disclosure Statement

A separate information disclosure statement disclosing the documents listed at end of the specification, in compliance with 37 CFR 1.98(b), is submitted herewith.

Specification Amendments

The specification is amended to correct an inadvertent clerical error in Table 1 at page 4, para. [00018] of the specification. Basis for the amendment is found in the sequence comparison of Figure 2. Paragraphs [00019-00021] at page 5 are also amended to correct an inadvertent reversal of the sequence identifiers for SorCS1 and SorCS3. The skilled person would readily recognize the true identity of these genes, as the sequences of each was available before the filing date of the application.

In the Brief Description of the Drawings, Figure 2 is amended to recite sequence identifiers for the sequences set forth therein.

To comply with sequence rules 37 CFR 1.821-1.825, applicants submitted herewith (1) a substitute sequence listing in paper and computer readable form; (2) a statement that the content of the sequence listing information recorded in the CRF is identical to the paper copy; and (3) an amendment directing entry of the sequence listing into the application. With the above amendments to the specification no new matter is added.

Claim Amendments

Amended Claims 1-3, drawn to a method of assessing susceptibility to type 2 diabetes (referred to herein as 'T2D') refer to the elected sequence (i.e., SorCS1). Amended Claim 1 affirmatively recites the steps of determining the SorCS1 cDNA sequence; deducing the encoded amino acid sequence; and comparing the deduced SorCS1 sequence with SEQ ID NO:4, such that a difference between the two sequences indicates T2D susceptibility. Amended Claim 2 recites the steps of determining the cDNA sequence of a subject in the SorCS1 gene; and comparing the determined SorCS1 cDNA sequence with SEQ ID NO:3, the difference between the two sequences indicating T2D susceptibility. Amended Claim 3 clarifies that a difference in the amino acid sequence observed and SEQ ID NO:4 indicates T2D susceptibility. No new matter is added. Support for these amendments is found, for example, at page 3-5 of the specification.

Newly added method Claim 9 further defines the scope of Claim 1 by affirmatively reciting that a mutation at position 52 of the SorCS1b isoform is indicative of a subject's susceptibility to developing type 2 diabetes. Dependent Claims 10 and 11 further define the type of mutation.

Claim Rejections - 35 USC §112, 1st ¶

Claims 1-3 stand rejected under 35 USC §112, 1st ¶ for allegedly lacking written description. The Examiner asserts

> "[t]he specification teaches that SorCS1 cDNA and amino acid sequence are SEQ ID NOS 1 and 2 respectively, however a search of each sequence reveals that such are the sequences for SorCS3." (See page 10, last ¶ of the present Office Action).

At the outset, the Examiner is correct in pointing out that SEQ ID NOs: 1 and 2 do not represent the SorCS1 cDNA and amino acid sequence, respectively. Applicants submit that they inadvertently reversed the sequence identifiers for SorCS1 and SorCS3. The specification is amended herein to reflect the correct sequence identifiers for human SorCS1 ("b" isoform, i.e., SorSC1b) cDNA and amino acid sequence, SEQ ID NOs: 3 and 4, respectively. It is believed that one of ordinary skill in the art would readily recognize the true identity of these genes, as the sequence of each was available before the filing date of the application.

Next, the Examiner asserts at the top of page 11 that "[t]he specification provides no teaching or working examples of any mutations in any portion of the SorSC1 gene in human...." Applicants do not agree with this assertion and submit that the written description requirement for this application is fully satisfied because the specification describes the structure of SorCS1 and its various isoforms in both mice and humans. Specifically, the application describes (1) the mouse SorCS1b cDNA and protein sequence (SEQ ID NO: 12); (2) the corresponding human SorCS1b cDNA and protein sequence (SEQ ID NO: 3 and 4, respectively); and (3) a predictable correlation between a mutation in the mouse and human SorCS1b sequences (i.e., conserved threonine residue at position 52), which is an indicator for a subject's susceptibility for developing T2D.

For example, Figure 2 (amended herein to include the sequence identifiers for SEQ ID NOs: 5-14) is a sequence comparison structurally describing the amino acid sequences for human SorCS1 (hCS1 1168 aa) and mouse SorCS1 (mCS1a 1147 aa; mCS1b 1167 aa; and mCS1c 1178 aa). In fact, Figure 2 shows a 91% sequence identity for mCS1a and hCS1; a 93% sequence identity for mCS1b and hCS1 (the "b" isoform); and a 90% sequence identity for mCS1c and hCS1.

Furthermore, the specification sets forth at page 5, paragraph [00019] that the genomic and cDNA sequences of human SorCS1 were known to those of ordinary skill in the art at the time of filing. The specification incorporates by reference the human SorCS1 cDNA sequence (GenBank Accession No. NM_052918) and amino acid sequence (GenBank Accession No. NP_443150). The specification also discloses that the mouse SorCS1b (mSorCS1b) and human SorCs1 (hSorcs1., the "b" isoform) in Figure 2 are highly homologous (i.e., 93% sequence identity). This degree of identity between the mouse and human SorCS1 coding region is sufficient to soundly predict that applicants' genetic evidence from the congenic mouse model is predictive of the same genetic phenomenon (i.e., susceptibility to T2D) in humans.

Next, the Examiner asserts "[t]he specification asserts at page 3 that the SorCS1 gene in mice is 'directly analogous' to the human gene, however this statement is unclear." Applicants do not agree with this assertion because at the time of filing, it was well known that analogous genes referred to genes similar in function but different in evolutionary origin (i.e., mouse and human). Thus, the meaning of the phrase "directly analogous" is clear.

In this regard, the Examiner indicates on page 11 of the present Office Action that "[t]he specification teaches a mutation at position 50 from Thr to Ile, at position 1139 from Ser to Phe, and at position 1149 from Ser to Pro. In human, however, position 50 is Alanine, position 1139 is Glyerine, and position 1149 (in SEQ ID NOS 4) is Arginine." The Examiner is correct in pointing out this discrepancy to the applicants. It appears that applicants misnumbered the amino acid residue located at position 52 of both mouse and human SorCS1b. Table 1 is amended to correct the inadvertent misnumbering.

It is noted that amino acid residue 52 in the human SorCS1b sequence (see SEQ ID NO: 4 or SEQ ID NO: 14 in Fig. 2) directly corresponds to the mutation identified at position 52 of the mouse SorCS1, the "b" isoform of the protein. Applicants submit that the threonine residue at position 52 is conserved in both mouse SorCS1 (all three isoforms) and human SorCS1 ("b" isoform, SEQ ID NO:4). Thus, no new matter is added to the specification, since the SorCS1b sequences (mouse and human) in the Figure 2 were correct, merely misnumbered.

Furthermore, in regards to the activity of the SorCS1 protein, the specification discloses at pages [00033] that the SorCS1 protein is active in determining islet mass, insulin secretion in pancreatic beta cells or insulin degradation in the kidney or liver. Applicants submit that any of these will affect plasma insulin levels, which are altered in the congenic mice disclosed.

Next, the Examiner cites Hermey et al., (2003) JBC vol. 278, pg. 7390-7396 to show that different isoforms of SorCS1 exist, for which the specification allegedly provides no description. Examiner is correct in asserting that Hermey et al., discloses different human SorCS1 isoforms. Hermey et al. reports the identification of different human SorCS1 isoforms by using Murine SorCS1b cDNA (GenBankTM accession number AF195056) to screen a human brain cDNA library. For example, cloning of the human SorCS1b was made possible because the cytoplasmic domain is highly similar to that of the murine orthologue. Hermey et al., report that the human SorCS1b cDNA (GenBankTM accession number AF284756) encodes a 33 amino acid signal peptide followed by a 1135 amino acid type 1 receptor (see Fig. 1A) with 92% sequence identity to the murine SorCS1b protein. In fact, Hermey's disclosure supports applicants' position that one of skill in the art can use mouse SorCS1b cDNA to identify mutations in the human SorCS1b cDNA and can use its coding region to predict susceptibility to developing T2D. Accordingly, it is believed that the written description requirement is fully satisfied.

Next, Claims 1-3 stand rejected under 35 USC §112, 1st ¶ for allegedly lacking enablement. Specifically, the Examiner asserts that "the nature of the invention ... requires the knowledge of predictive associations between any polymorphism or mutation in any region of the human SorCS1 gene and susceptibility to developing type 2 diabetes." (see pg. 5 of the present office action). The Examiner also asserts that to practice the invention as claimed, one would have to establish that a predictive relationship exists between mutations in any region of the SorCS1 gene and type 2 diabetes in humans.

In response, applicants submit that the specification is fully enabling because it provides all of the structural and functional information necessary for one of skill to make a predictive association between (1) mouse and human SorCS1b protein and (2) a mutation in the SorCS1b protein and susceptibility to developing T2D.

Applicants were the first to establish that the SorCS1 gene is one of the genetic factors responsible for T2D and linked severe T2D to a 7MB segment of mouse chromosome 19. Next, applicants established that a predictable correlation exists between a structural alteration in the SorCS1b protein (mouse and human) and susceptibility for developing T2D in humans. To establish this correlation, applicants mapped 2 loci associated with diabetes susceptibility in mice. One locus on chromosome 16 was associated with a less severe form of diabetes and the second locus on chromosome 19 was associated with a more severe form of T2D. Applicants discovered that mice having the severe form inherited a 7 Mb segment of chromosome 19 from a parent and exhibited very high levels of plasma glucose, averaging 120 mg/dl. Applicants thus proceeded to characterize the genes and sequences in the 7 Mb region to identify a genetic element responsible for the differential in susceptibility to diabetes.

Applicants discovered that the alleles of all genes carried in the region by the more severely and less severely diabetic mice were the same except for the allele of the SorCS1 gene. Fig. 1 illustrates a genetic map of the genetic elements found in the 7 Mb region associated with the genetic difference. Applicants identified the region between map units 55 and 48 as carrying the genetic difference. Applicants determined that the more severely diabetic mice have an allele of the SorCS1 gene that differs at three amino acids from the allele of that same protein in mice with the less severe form of T2D (see Table 1). Specifically, applicants disclose that the threonine residue at position 52 in mouse and human SorCS1b (see sequence comparison of Fig.

2) is an evolutionarily conserved residue. It is also disclosed that a mutation of the threonine residue in that region is an indicator for a subject's susceptibility for developing T2D.

Applicants have discovered that the difference in susceptibility to diabetes resolved down to differences in the alleles of the gene for SorCS1. Since the same correlation that exists in mice also exists in humans, and since the analogous SorCS1 gene ("b" isoform) having a conserved threonine at amino acid residue 52 is found in mouse and humans, the same susceptibility to developing T2D should be found in humans and in mouse. (See page 3, [00015]). Thus, a predictive association between mouse and human SorCS1b protein and susceptibility to developing T2D is established in the present application.

It is further noted that, among the genes analyzed in mice, SorCS1 is the only gene for which applicants detected amino acid substitutions and expression level differences, identifying variation within the SorCS1 gene as underlying the T2D phenotype. Applicants believe that the SorCS1 gene is at least one of the sources of genetic susceptibility to T2D and allelic differences in this gene are alone sufficient to explain some of the genetic susceptibility to the disease. Based on this notion, it was predicted that human genetic tests could be performed to determine if a subject is genetically susceptible to T2D due to his or her SorCS1 gene allele. Thus, it is believed that the enablement requirement is fully satisfied.

Accordingly, applicants respectfully request that in view of these claim amendments and comments, the rejection be reconsidered, withdrawn and that a timely Notice of Allowance be issued in this case.

A petition for extension of time accompanies this response so the response will be deemed to have been timely filed. Please charge the fee to Deposit Account No. 17-0055. If any other fee is due or any other extension of time is required in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee to the Deposit Account No. 17-0055.

Respectfully submitted,

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